REMARKS

Claims 1-3 and 5-23 are pending in the application. All claims have been finally rejected.

Rejections

(1). Claims 1-3 stand rejected under 35 U.S.C. 103(a) as being unpatentable over US 4,089,432 to Crankshaw et al. in view of US 5,549,561 to Hjertman for the reasons of record.

(2). Claims 5-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 4,089,432 to Crankshaw et al in view of US 5,549,561 to Hjertman, further in view of US 6,481,435 to Hochrainer et al. for the reasons of record.

For the following reasons, given in reply to Examiner's "Response to Arguments" starting on page 5 of the Office Communication, Applicant respectfully submits that claims 1-3 are not obvious over the combined teachings of Crankshaw and Hjertman, and further that claims 5-23 are not obvious over Crankshaw et al. in view of Hjertman and further in view of US 6,481,435 to Hochrainer et al.

- 5 - The Examiner proposes that Crankshaw and Hjertman are directed to solving one and the same problem, namely "maintaining a separation between volatile substances contained in a single device until needed for patient application".

It is respectfully submitted, however, that such is not the case.

Crankshaw relates to a closure structure for a two-compartment vial in which a **lyophilized** medication and a **solvent** may be held in complete independence from each other until it becomes desirable to use the medication.

Crankshaw's invention is directed to solving the problem that *"...in order to dislodge the center plug from between the compartments so that the solvent can be mixed with the medication, it is necessary to depress the stopper which is partially disposed in the neck of the vial and projects somewhat beyond said neck. The **problem** is that the projecting portion of the stopper tends to bulge radially outwardly when it is urged into the neck*

and therefore opposes insertion of the stopper into the neck. (...) If the stopper is made from less flexible material then leakage of the solvent past the stopper readily occurs." (column 1, lines 26-39 of Crankshaw, emphasis added).

Hjertman's invention on the other hand is directed to solving the following problems:

"The solid substance in the front chamber of a dual-chamber injection cartridge is usually surrounded by a gaseous phase, which is usually air. This means that when the liquid phase is made to flow from the rear chamber through the bypass channel into the front chamber to be mixed with the solid substance, air bubbles will be formed and will adhere to the internal wall of the cartridge. The ***problem*** *is aggravated by the fact that said internal wall has usually been made hydrophobic to facilitate the movement of the movable walls. (...) In all cases, however, the air bubbles formed are very difficult to remove."* (paragraph bridging columns 1 and 2 of Hjertman, emphasis added)

"The presence of air bubbles in the preparation to be injected is highly undesirable. The most important ***problem*** *is that if air bubbles above a certain critical size are injected, they may block the capillary blood vessels and give rise to very serious consequences. (...) As the air bubbles are compressible, this leads to a decreased accuracy in the dosing of the preparation. Furthermore, due to the magnifying-glass effect of the liquid in the cartridge, the small air bubbles adhering to the internal wall will look much bigger, and this gives rise to anxiety in the user, who is usually aware of the risks associated with the presence of big air bubbles in a preparation for injection."* (column 2, lines 14-28 of Hjertman, emphasis added)

Neither Crankshaw nor Hjertman indicates or suggests that the problem resides in maintaining separation between volatile substances contained in a single device until needed for patient application. As may be seen from the portions of Crankshaw's and Hjertman's disclosures set forth above, the problems actually addressed by them, are clearly different from that alleged by the Examiner and from each other.

The present invention relates to an article of manufacture for administration of a pharmaceutical composition in the form of a ***ready-to-use aqueous suspension***.

The **problem** addressed by the present invention relates to "controlled flocculation", which is a well-known approach to stabilizing an aqueous suspension formulation of a drug, particularly a poorly soluble drug. According to this approach, an aqueous medium or vehicle for the drug is provided that permits aggregation of particles of the drug to form a floc. A desirable floc is one that tends to settle, but is readily resuspended with slight agitation and remains in uniform suspension during a period of time long enough to permit administration, for example parenterally, to a subject. Controlled flocculation of a poorly soluble drug generally requires the presence in the aqueous medium of one or more wetting agents and one or more suspending agents. (see paragraph [003] of the present published application US 2004/0039366, emphasis added.)

It has, however, been found that where an aqueous suspension includes certain **wetting and suspending agents**, the suspension tends to show a decline in stability with time. In many instances this decline is due to a process known as "oxidative degradation."

By reducing or minimizing exposure of the formulation to oxygen, **problems** of oxidative degradation can be substantially overcome. For example, if an injectable formulation is packaged in an airtight container such as a vial having little or no headspace acting as a reservoir of gaseous oxygen, i.e., if the container is substantially filled with the formulation, oxidative degradation is likely to be minimized. This can be an acceptable way to package a formulation that does not require agitation to homogenize the formulation prior to use, for example a formulation in the form of an aqueous solution. However, the lack of headspace becomes a serious **problem** in the case of an aqueous suspension formulation exhibiting controlled flocculation, because it greatly impedes the ability to agitate the formulation, for example by shaking the container, to resuspend a settled floc and provide a fine homogeneous suspension for parenteral injection. Where the formulation is packaged in a unit-dose container such as a vial, it is particularly important to be able to resuspend substantially all of a drug deposit so that the full dose can be administered. (see paragraph [0010] of the present application publication, emphasis added).

- 6 - It should be clear from the discussion above that, even if the artisan were to combine the teachings of Crankshaw on the one hand and Hjertman on the other,

merely because they both belong to the same very **broad and general** field of "injection vials", but *despite* the fact that **they are directed to solving different problems** and *despite* the fact that there is **no pointer** in either of the documents to the other one, such a combination would still not address, much less resolve, the problems which the present invention is directed to solve, namely to allow, or at least improve, resuspension of a settled floc occurring when using the "controlled flocculation" approach to stabilizing a ready-to-use aqueous suspension formulation of poorly soluble drugs for parenteral administration.

The Examiner cites *Ex parte Thibault*, 164 USPQ 666, 667 (Bd. App. 1969) for the proposition that the "recitation of the contents of an apparatus during an intended use of an apparatus is of little significance in determining the patentability of the apparatus claim."
The claims of the present application, however, are all directed to "an article of manufacture" - that is a product, a physical thing.
The cited Thibault decision is mentioned in MPEP 2115 "Material or Article Worked Upon by Apparatus" - the last paragraph of which states:
"Note that this line of cases is **limited** to claims directed to machinery which works upon an article or material in its intended use. ***It does not apply to product claims or kit claims*** (i.e., claims directed to a plurality of articles grouped together as a kit)." (emphasis added)

This is quite logical as it would indeed be strange if the contents of an article of manufacture would always be of no significance in determining patentability.

- 7 - The Examiner continues with alleging that the claimed article of manufacture would be ***identical*** to the device disclosed by Crankshaw. As best understood by the Applicant this misapprehension must be based on the idea that features such as "an aqueous suspension" would not be a structural feature - but somehow a functional one. The Applicant, however, is of the opinion that "an aqueous suspension" is to be understood to be a structural feature, not a functional one.

The middle paragraph of MPEP 2114 reads as follows:
A claim containing a "recitation with respect to the manner in which a claimed apparatus is intended to be employed does not differentiate the claimed apparatus from a prior art

apparatus" if the prior art apparatus teaches all the structural limitations of the claim. *Ex parte Masham,* 2 USPQ2d 1647 (Bd. Pat. App. & Inter. 1987) (The preamble of claim 1 recited that the apparatus was "for mixing flowing developer material" and the body of the claim recited "means for mixing ..., said mixing means being stationary and completely submerged in the developer material". The claim was rejected over a reference which taught all the structural limitations of the claim for the intended use of mixing flowing developer. However, the mixer was only partially submerged in the developer material. The Board held that the amount of submersion is immaterial to the structure of the mixer and thus the claim was properly rejected.) (emphasis in the original).

Apart from the fact that the claims on file in the present application are all directed to "an article of manufacture" (a product, a physical thing), the claims do not contain any recitation with respect to the manner in which the claimed an article of manufacture is intended to be employed. And the claimed article of manufacture is indeed differentiated from the prior art because the prior art does not teach all the structural limitations of the claim, as - if for no other reason - the cited prior art does not disclose any chamber that is substantially filled with any aqueous suspension.

- 8 - The Examiner alleges that Hjertman discloses that the apparatus must provide sufficient headspace for the liquid product to be mixed with the solid product and therefore does not teach away from the present invention as submitted by Applicant.

To better understand what Hjertman teaches, the Examiner's attention is drawn to the disclosure at column 4, lines 25-53 of Hjertman, which reads as follows:

"In the front chamber, the amount of gas should be as low as possible, as this decreases the solubility requirements. This means that ***the empty space in the front chamber should be as small as possible***, so that the risk that bubbles are formed will be decreased. However, ***this works against the requirement that there must be sufficient room for the liquid product which is to be mixed with the solid product***. A smaller space will also lead to a higher pressure in the front chamber when the liquid is introduced. This is undesirable, as more gas will be dissolved in the liquid at the higher pressure, but will be liberated again when the pressure is released, as occurs

when the preparation is injected. ***However, through an embodiment of the cartridge of the present invention, this problem is eliminated.***

"Thus, ***in a preferred embodiment*** of the invention, the cartridge is provided with means for relieving any superatmospheric pressure formed and maintain a substantially constant pressure in the front chamber at the mixing of the solid product with the liquid product. (...) ***In the most preferred embodiment***, however, a third, fluid-sealing movable wall is arranged in the front chamber immediately in front of the solid product". (emphasis added)

Accordingly, what Hjertman says is that he is aware that his inventive features conflict with the need for headspace for mixing purposes - but this does not cause him to teach or suggest any reintroduction of such headspace, but an alternative solution. This must reasonably be a ground for taking a position that Hjertman "teaches away" from the present invention.

- 9 - Finally, it is appreciated that the Examiner does not elaborate on Hochrainer. As previously submitted, Hochrainer does not discloses a two-chamber vial in the meaning of the present invention and can therefore not lead the skilled person towards the invention as claimed, either alone, or together with the combined teachings of Crankshaw and Hjertman.

Accordingly, reconsideration and withdrawal of the rejection of Claims 1-3 and the rejection of claims 5-23 is respectfully requested.

Respectfully submitted,

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